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PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No. PU60160P

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TITLE OF THE INVENTION (280 characters max)

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ENCLOSED APPLICATION PARTS (check all that apply)

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METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

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Respectfully submitted,
Signature: **Laura K. Madden**

Date: 03/27/03

Registration No.: 48,352

☐ Additional inventors are being named on separately numbered sheets attached hereto.

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PU60160p

TITLE

Antibacterial Agents

FIELD OF THE INVENTION

This invention relates to novel compounds, compositions containing them and their use as antibacterials.

BACKGROUND OF THE INVENTION

The emergence of pathogens resistant to known antibiotic therapy is becoming a serious global healthcare problem (Chu, et al., (1996) *J. Med. Chem.*, 39: 3853-3874). Thus, there is a need to discover new broad spectrum antiobiotics useful in combating multidrug-resistant organisms. Importantly, it has now been discovered that certain compounds have antibacterial activity, and, therefore, may be useful for the treatment of bacterial infections in mammals, particularly in humans.

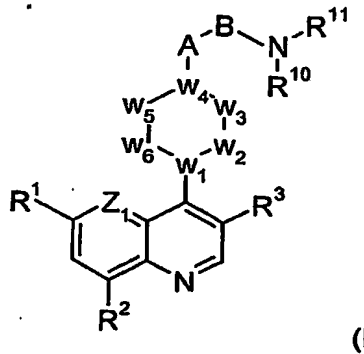
WO0208224, WO0256882, WO02/40474 and WO02/72572 disclose quinoline and naphthyridine derivatives having antibacterial activity.

SUMMARY OF THE INVENTION

This invention comprises compounds of the formula (I), as described hereinafter, which are useful in the treatment of bacterial infections. This invention is also a pharmaceutical composition comprising a compound according to formula (I) and a pharmaceutically acceptable carrier. This invention is also a method of treating bacterial infections in mammals, particularly in humans.

DETAILED DESCRIPTION OF THE INVENTION

This invention provides a compound of formula (I) or a pharmaceutically acceptable derivative thereof:



(I)

wherein:

Z_1 is N or CR^{1a};

R^1 and R^{1a} are independently hydrogen; hydroxy; (C_{1-6})alkoxy unsubstituted or substituted by (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; nitro; azido; cyano; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups; or R^1 and R^{1a} may together form ethylenedioxy;
with the proviso that when Z_1 is CR^{1a} then R^1 is not H;

R^2 is H or halogen;
with the proviso that when Z_1 is N, then R^2 is H;

R^3 is hydrogen; halogen; hydroxy; cyano; CF_3; nitro; azido; acyl; aryl; heteroaryl; CO_2H; acyoxy; acylthio; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{3-7})cycloalkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethoxy; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; or arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

w_1 is N, C, or CR^4;
w_2 is C=O, CR^4, or CR^4R^5;
w_3 is C=O or CR^4R^5;

w_4 is N or CR^4;
w_5 is C=O or CR^4R^5;
w_6 is C=O, CR^4, or CR^4R^5;

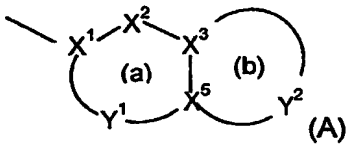
each R^4 and R^5 is independently hydrogen; halogen; hydroxy; cyano; CF_3; nitro; azido; acyl; aryl; heteroaryl; CO_2H; acyoxy; acylthio; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{3-7})cycloalkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethoxy; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; or arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups; or two R^5 groups are joined together to form bicycloheptane;

A is CR^6R^7 or C(O);
B is CR^8R^9 or C(O);

R^6, R^7, R^8, and R^9 are independently hydrogen; halogen; hydroxy; cyano; CF_3; nitro; azido; acyl; aryl; heteroaryl; CO_2H; acyoxy; acylthio; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{3-7})cycloalkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethoxy; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; or arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

R^{10} is hydrogen; aryl; heteroaryl; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, piperazinyl, morpholino, guanidino, or amidino, any of which is unsubstituted or N-substituted by one or two aryl, heteroaryl, halogen, cyano, CF_3, unsubstituted (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, arylsulphonyl, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy, or (C_{1-6})alkylsulphonyloxy, so long as the substitution does not lead to an unstable compound; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; hydroxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenylcarbonyl; (C_{1-6})alkoxycarbonyl; CO_2H; or CF_3;

R^{11} is a group -U-R^{12} where R^{12} is a substituted or unsubstituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_X$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_X$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_X$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; trifluoromethoxy; nitro; cyano; carboxy; amino or aminocarbonyl unsubstituted or substituted by (C_{1-4})alkyl.

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl unsubstituted or substituted by hydroxy, carboxy, (C_{1-4})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; or aminocarbonyl wherein the amino group is optionally substituted (C_{1-4})alkyl;

each x is independently 0, 1 or 2;
U is CO, SO_2, CH_2, or $CR^{16}R^{17}$;

R^{16} and R^{17} are independently selected from H; aryl; heteroaryl; (C_{1-6})alkyl; (C_{1-6})alkyl substituted by (C_{1-6})alkoxy, hydroxy, amino, piperidyl, piperazinyl, morpholino, guanidino, or amidino, any of which is substituted or N-substituted by one or two H, aryl, heteroaryl, halogen, cyano, CF_3, (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, arylsulphonyl, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy, or (C_{1-6})alkylsulphonyloxy, so long as the substitution does not lead to an unstable compound; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; hydroxy-substituted(C_{1-6})alkyl; amino-substituted(C_{1-6})alkyl, which is N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, or arylsulphonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenylcarbonyl; (C_{1-6})alkoxycarbonyl; CO_2H; or CF_3;

Also included in this invention are pharmaceutically acceptable addition salts, complexes or prodrugs of the compounds of this invention. Prodrugs are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo*.

The invention also provides a pharmaceutical composition, in particular for use in the treatment of bacterial infections in mammals, particularly humans, comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The invention further provides a method of treatment of bacterial infections in mammals, particularly in humans, which method comprises the administration to a mammal in need of such treatment an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

Preferably R^1 is F, Cl, OCH_3, methyl, or SCH_3. Most preferably R^1 is F, Cl, or OCH_3.

Preferably, R^{1a} is H, OCH_3, or $OCH_2CH_2OCH_3$.

Preferably, R^2 is H or F. Most preferably R^2 is H.

Preferably, R^3 is Cl or F.

Preferably w_1 is N or CR^4.

Preferably w_2, w_3, w_5, and w_6 are CR^4R^5.

Preferably each R^4 is independantly H, methyl, OH, -COOH, NH_2, or $-CH_2OH$.

Preferably R^5 is H.

Preferably A is CR^6R^7.

Preferably B is CR^8R^9.

R6 and R8 are preferably H.

Preferably R7 is H or OH.

Preferably R9 is H or OH.

Preferably R^{10} is H.

The group –U- is preferably $–CH_2-$.

Preferably R^{12} is an aromatic heterocyclic ring (A) having 8-11 ring atoms including 2-4 heteroatoms of which at least one is N or NR^{13}, in which preferably Y^2 contains 2-3 heteroatoms, one of which is S and 1-2 are N, with one N bonded to X^3.

Alternatively and preferably the heterocyclic ring (A) has ring (a) aromatic selected from optionally substituted benzo and pyrido and ring (b) non-aromatic and Y^2 has 3-5 atoms including a heteroatom bonded to X^5 selected from NR^{13}, O or S and NHCO bonded via N to X^3, or O bonded to X^3. Examples of rings (A) include optionally substituted:

<u>(a) and (b) aromatic</u>

1H-pyrrolo[2,3-b]-pyridin-2-yl, 1H-pyrrolo[3,2-b]-pyridin-2-yl, 3H-imidazo[4,5-b]-pyrid-2-yl, 3H-quinazolin-4-one-2-yl, benzimidazol-2-yl, benzo[1,2,3]-thiadiazol-5-yl, benzo[1,2,5]-oxadiazol-5-yl, benzofur-2-yl, benzothiazol-2-yl, benzo[b]thiophen-2-yl, benzoxazol-2-yl, chromen-4-one-3-yl, imidazo[1,2-a]pyridin-2-yl, imidazo-[1,2-a]-pyrimidin-2-yl, indol-2-yl, indol-6-yl, isoquinolin-3-yl, [1,8]-naphthyridine-3-yl, oxazolo[4,5-b]-pyridin-2-yl, quinolin-2-yl, quinolin-3-yl, quinoxalin-2-yl, indan-2-yl, naphthalen-2-yl, 1,3-dioxo-isoindol-2yl, benzimidazol-2-yl, benzothiophen-2-yl, 1H-benzotriazol-5-yl, 1H-indol-5-yl, 3H-benzooxazol-2-one-6-yl, 3H-benzooxazol-2-thione-6-yl, 3H-benzothiazol-2-one-5-yl, 3H-quinazolin-4-one-2-yl, 3H-quinazolin-4-one-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-3-yl, benzo[1,2,3]thiadiazol-6-yl, benzo[1,2,5]thiadiazol-5-yl, benzo[1,4]oxazin-2-one-3-yl, benzothiazol-5-yl, benzothiazol-6-yl, cinnolin-3-yl, imidazo[1,2-a]pyridazin-2-yl, imidazo[1,2-b]pyridazin-2-yl, pyrazolo[1,5-a]pyrazin-2-yl, pyrazolo[1,5-a]pyridin-2-yl, pyrazolo[1,5-a]pyrimidin-6-yl, pyrazolo[5,1-c][1,2,4]triazin-3-yl, pyrido[1,2-a]pyrimidin-4-one-2-yl, pyrido[1,2-a]pyrimidin-4-one-3-yl, quinazolin-2-yl, quinoxalin-6-yl, thiazolo[3,2-a]pyrimidin-5-one-7-yl, thiazolo[5,4-b]pyridin-2-yl, thieno[3,2-b]pyridin-6-yl, thiazolo[5,4-

b]pyridin-6-yl, 4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl, 1-oxo-1,2-dihydro-isoquinolin-3-yl, thiazolo[4,5-b]pyridin-5-yl, [1,2,3]thiadiazolo[5,4-b]pyridin-6-yl, 2H-isoquinolin-1-one-3-yl

(a) is non aromatic

(2S)-2,3-dihydro-1H-indol-2-yl, (2S)-2,3-dihydro-benzo[1,4]dioxine-2-yl, 3-(R,S)-3,4-dihydro-2H-benzo[1,4]thiazin-3-yl, 3-(R)-2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 3-(S)-2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-3-yl, 2,3-dihydro-benzo[1,4]dioxan-2-yl, 3-substituted-3H-quinazolin-4-one-2-yl, 2,3-dihydro-benzo[1,4]dioxan-2-yl, 1-oxo-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl.

(b) is non aromatic

1,1,3-trioxo-1,2,3,4-tetrahydro-1 λ^6-benzo[1,4] thiazin-6-yl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2-oxo-2,3-dihydro-benzooxazol-6-yl, 4H-benzo[1,4]oxazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl), 4H-benzo[1,4]thiazin-3-one-6-yl (3-oxo-3,4-dihydro-2H-benzo[1,4]thiazin-6-yl), 4H-benzo[1,4]oxazin-3-one-7-yl, 4-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepine-7-yl, 5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidin-6-yl, benzo[1,3]dioxol-5-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]thiazin-7-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl, 2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl, 2,3-dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl, 6,7-dihydro-[1,4]dioxino[2,3-d]pyrimidin-2-yl, 3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl, 2-oxo-2,3-dihydro-1H-pyrido[3,4-b][1,4]oxazin-7-yl, 2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl, 6-oxo-6,7-dihydro-5H-8-thia-1,2,5-triaza-naphthalen-3-yl, 3,4-dihydro-2H-benzo[1,4]oxazin-6-yl, 3-substituted-3H-benzooxazol-2-one-6-yl, 3-substituted-3H-benzooxazole-2-thione-6-yl, 3-substituted-3H-benzothiazol-2-one-6-yl, 2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl, 3,4-dihydro-2H-benzo[1,4]thiazin-6-yl, 3,4-dihydro-1H-quinolin-2-one-7-yl, 3,4-dihydro-1H-quinoxalin-2-one-7-yl, 6,7-dihydro-4H-pyrazolo[1,5-a]pyrimidin-5-one-2-yl, 5,6,7,8-tetrahydro-[1,8]naphthyridin-2-yl, 2-oxo-3,4-dihydro-1*H*-[1,8]naphthyridin-6-yl, 3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazin-6-yl.

R^{13} is preferably H if in ring (a) or in addition (C_{1-4})alkyl such as methyl or isopropyl when in ring (b). More preferably, in ring (b) R^{13} is H when NR^{13} is bonded to X^3 and (C_{1-4})alkyl when NR^{13} is bonded to X^5.

R^{14} and R^{15} are preferably independently selected from hydrogen, halo, hydroxy, (C_{1-4}) alkyl, (C_{1-4})alkoxy, trifluoromethoxy; nitro, cyano, aryl(C_{1-4})alkoxy and (C_{1-4})alkylsulphonyl.

More preferably R^{15} is hydrogen.

More preferably each R^{14} is selected from hydrogen, chloro, fluoro, hydroxy, methyl, methoxy, trifluoromethoxy, benzyloxy, nitro, cyano and methylsulphonyl. Most preferably R^{14} is selected from hydrogen, hydroxy, fluorine or nitro. Preferably 0-3 groups R^{14} are substituents other than hydrogen.

Preferred groups R^{12} include:

[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl,
1H-Pyrrolo[2,3-b]pyridin-2-yl,
2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-6-yl,
2,3-Dihydro-[1,4]dioxino[2,3-b]pyridin-7-yl,
2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl,
2,3-dihydro-benzo[1,4]dioxin-6-yl,
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]oxazin-7-yl,
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl,
3,4-dihydro-2H-benzo[1,4]oxazin-6-yl,
3-Methyl-2-oxo-2,3-dihydro-benzooxazol-6-yl,
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl,
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl,
4H-benzo[1,4] thiazin-3-one-6-yl,
4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl,
6-nitro-benzo[1,3]dioxol-5-yl,
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl,
8-Hydroxy-1-oxo-1,2-dihydro-isoquinolin-3-yl,
8-hydroxyquinolin-2-yl,
benzo[1,2,3]thiadiazol-5-yl,
benzo[1,2,5]thiadiazol-5-yl,
benzothiazol-5-yl,
thiazolo-[5,4-b]pyridin-6-yl,
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl,
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl,
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl, and
2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-7-yl.

Most preferred groups R^{12} include:

benzo[1,2,5]thiadiazol-5-yl,
4H-benzo[1,4] thiazin-3-one-6-yl,
2,3-dihydro-benzo[1,4]dioxin-6-yl,

benzo[1,2,3]thiadiazol-5-yl,
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl,
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl,
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl,
2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl,
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl,
[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl,
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl,
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl,
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl, and
2-oxo-2,3-dihydro-1*H*-pyrido[3,4-*b*][1,4]thiazin-7-yl.

Most especially preferred groups R^{12} include:
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl,
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazin-6-yl, and
2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl.

Preferred compounds of this invention include:
6-({2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-
{2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}amine;

6-({2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-
{2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}amine;

6-({2-[1-(3-chloro-6-methoxy-[1,5]quinolin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(3-chloro-6-methoxy-[1,5]quinolin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine;

6-({2-[1-(3-chloro-6-methoxy-[1,5]naphthyridin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(3-chloro-6-methoxy-[1,5]naphthyridin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine;

6-({2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)-{2-[4-(6-methoxyquinolin-4-yl)piperizin-1-yl]ethyl}amine;

6-({2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)-{2-[4-(6-methoxynaphthyridin-4-yl)piperizin-1-yl]ethyl}amine;

6-({2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine;

6-({2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine; and

6-({2-[4-(6-Methoxy-[1,5]naphthyridin-4-yl)-3,6-dihydro-2 H –pyridin-1-yl]-2-oxo-ethylamino}-methyl) –4 H –pyrido[3,2-b][1,4]thiazin-3-one;
or a pharmaceutically acceptable salt thereof.

Unless otherwise defined, the term (C_{1-6})alkyl when used alone or when forming part of other groups (such as the 'alkoxy' group) includes substituted or unsubstituted, straight or branched chain alkyl groups containing 1 to 6 carbon atoms. Examples of (C_{1-3})alkyl include methyl, ethyl, n-propyl, and isopropyl groups.

The term (C_{2-6})alkenyl means a substituted or unsubstituted alkyl group of 2 to 6 carbon atoms, wherein one carbon-carbon single bond is replaced by a carbon-carbon double bond. Examples of (C_{2-6})alkenyl include ethylene, 1-propene, 2-propene, 1-butene, 2-butene, and isobutene. Both cis and trans isomers are included.

The term (C_{3-7})cycloalkyl refers to subsituted or unsubstituted carbocyclic system of three to seven carbon atoms, which may contain up to two unsaturated carbon-carbon bonds. Examples of (C_{3-7})cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, and cycloheptyl.

Unless otherwise defined, suitable substituents for any (C_{1-6})alkyl, (C_{1-6})alkoxy, (C_{2-6})alkenyl, and (C_{3-7})cycloalkyl groups includes up to three substituents selected from

the group consisting of hydroxy, halogen, nitro, cyano, carboxy, amino, amidino, sulphonamido, unsubstituted (C_{1-3})alkoxy, trifluromethyl, acyloxy.

Halo or halogen includes fluoro, chloro, bromo and iodo.

Haloalkyl moieties include 1-3 halogen atoms.

Unless otherwise defined, the term "heterocyclic" as used herein includes optionally substituted aromatic and non-aromatic, single and fused, rings suitably containing up to four hetero-atoms in each ring selected from oxygen, nitrogen and sulphur, which rings may be unsubstituted or C-substituted by, for example, up to three groups selected from (C_{1-4})alkylthio; halo; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy; hydroxy, (C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano, carboxy; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl; or aminosulphonyl wherein the amino group is optionally substituted by (C_{1-4})alkyl or (C_{2-4})alkenyl.

Each heterocyclic ring suitably has from 4 to 7, preferably 5 or 6, ring atoms. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring.

Compounds within the invention containing a heterocyclyl group may occur in two or more tautometric forms depending on the nature of the heterocyclyl group; all such tautomeric forms are included within the scope of the invention.

Where an amino group forms part of a single or fused non-aromatic heterocyclic ring as defined above suitable optional substituents in such substituted amino groups include H; trifluoromethyl; (C_{1-4})alkyl optionally substituted by hydroxy, (C_{1-4})alkoxy, (C_{1-4})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl;

When used herein the term "aryl", includes optionally substituted phenyl and naphthyl.

Aryl groups may be optionally substituted with up to five, preferably up to three, groups selected from (C_{1-4})alkylthio; halo; halo(C_{1-4})alkoxy; halo(C_{1-4})alkyl; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy;
hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; nitro; cyano; carboxy; amino or aminocarbonyl optionally substituted by (C_{1-4})alkyl; (C_{1-4})alkylsulphonyl; (C_{2-4})alkenylsulphonyl.

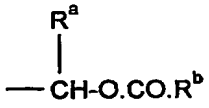
The term "acyl" includes formyl and (C_{1-4})alkylcarbonyl group.

Some of the compounds of this invention may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

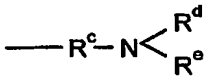
Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably from 10 to 59% of a compound of the formula (I) or pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives of the above-mentioned compounds of formula (I) include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, p-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid or tartaric acids. Compounds of formula (I) may also be prepared as the N-oxide. Compounds of formula (I) having a free carboxy group may also be prepared as an *in vivo* hydrolysable ester. The invention extends to all such derivatives.

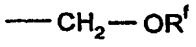
Examples of suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming groups include those forming esters which break down readily in the human body to leave the parent acid or its salt. Suitable groups of this type include those of part formulae (i), (ii), (iii), (iv) and (v):



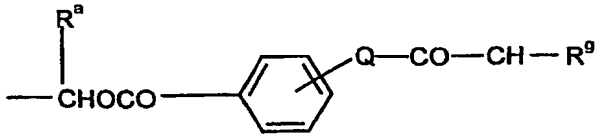
(i)



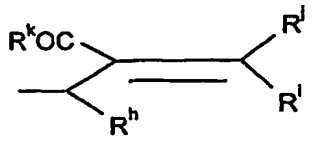
(ii)



(iii)



(iv)

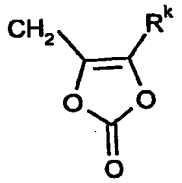


(v)

wherein R^a is hydrogen, (C_{1-6}) alkyl, (C_{3-7}) cycloalkyl, methyl, or phenyl, R^b is (C_{1-6}) alkyl, (C_{1-6}) alkoxy, phenyl, benzyl, (C_{3-7}) cycloalkyl, (C_{3-7}) cycloalkyloxy, (C_{1-6}) alkyl (C_{3-7}) cycloalkyl, 1-amino (C_{1-6}) alkyl, or 1-$(C_{1-6}$ alkyl)amino (C_{1-6}) alkyl; or R^a and R^b together form a 1,2-phenylene group optionally substituted by one or two methoxy groups; R^c represents (C_{1-6}) alkylene optionally substituted with a methyl or ethyl group and R^d and R^e independently represent (C_{1-6}) alkyl; R^f represents (C_{1-6}) alkyl; R^g represents hydrogen or phenyl optionally substituted by up to three groups selected from halogen, (C_{1-6}) alkyl, or (C_{1-6}) alkoxy; Q is oxygen or NH; R^h is hydrogen or (C_{1-6}) alkyl; R^i is hydrogen, (C_{1-6}) alkyl optionally substituted by halogen, (C_{2-6}) alkenyl, (C_{1-6}) alkoxycarbonyl, aryl or heteroaryl; or R^h and R^i together form (C_{1-6}) alkylene; R^j represents hydrogen, (C_{1-6}) alkyl or (C_{1-6}) alkoxycarbonyl; and R^k represents (C_{1-8}) alkyl, (C_{1-8}) alkoxy, (C_{1-6}) alkoxy(C_{1-6})alkoxy or aryl.

Examples of suitable *in vivo* hydrolysable ester groups include, for example, acyloxy(C_{1-6})alkyl groups such as acetoxymethyl, pivaloyloxymethyl, α-acetoxyethyl, β-pivaloyloxyethyl, 1-(cyclohexylcarbonyloxy)prop-1-yl, and (1-aminoethyl)carbonyloxymethyl; (C_{1-6})alkoxycarbonyloxy(C_{1-6})alkyl groups, such as ethoxycarbonyloxymethyl, α -ethoxycarbonyloxyethyl and propoxycarbonyloxyethyl; di(C_{1-6})alkylamino(C_{1-6})alkyl especially di(C_{1-4})alkylamino(C_{1-4})alkyl groups such as dimethylaminomethyl, dimethylaminoethyl, diethylaminomethyl or diethylaminoethyl; 2-((C_{1-6})alkoxycarbonyl)-2-(C_{2-6})alkenyl groups such as 2-(isobutoxycarbonyl)pent-2-enyl and 2-(ethoxycarbonyl)but-2-enyl; lactone groups such as phthalidyl and dimethoxyphthalidyl.

A further suitable pharmaceutically acceptable *in vivo* hydrolysable ester-forming group is that of the formula:



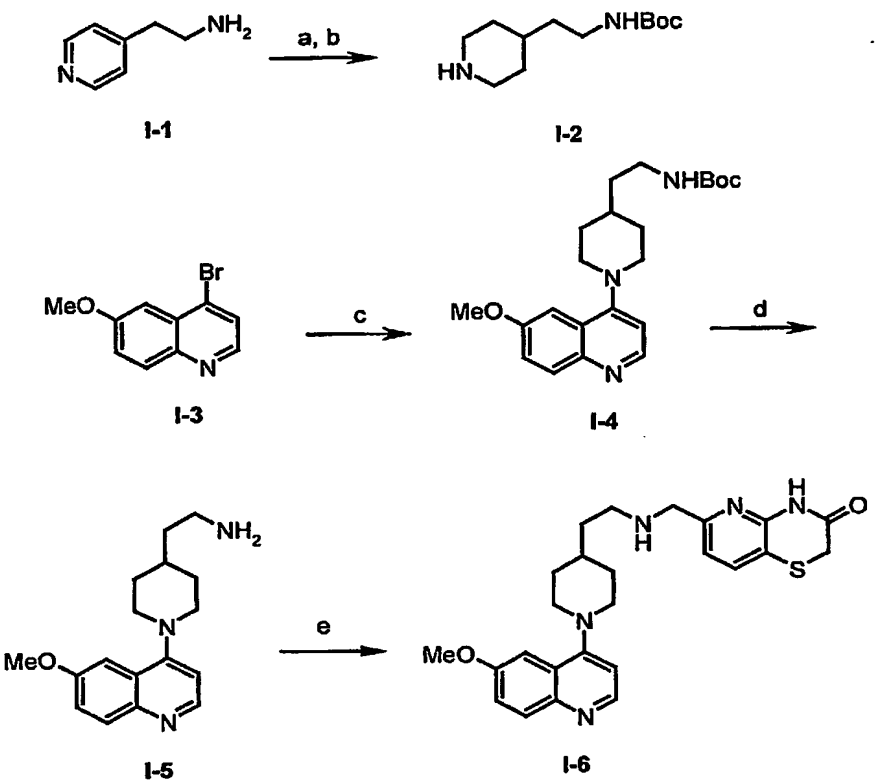
wherein R^k is hydrogen, C_{1-6} alkyl or phenyl.

R is preferably hydrogen.

Compounds of formula (I) may also be prepared as the corresponding N-oxides. Certain of the compounds of formula (I) may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes all such forms, in particular the pure isomeric forms. For example the invention includes compound in which an A-B group CH(OH)-CH_2 is in either isomeric configuration, the *R*-isomer is preferred. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

The compounds of the present invention were prepared by the methods illustrated in Schemes I, II, and III.

Scheme I

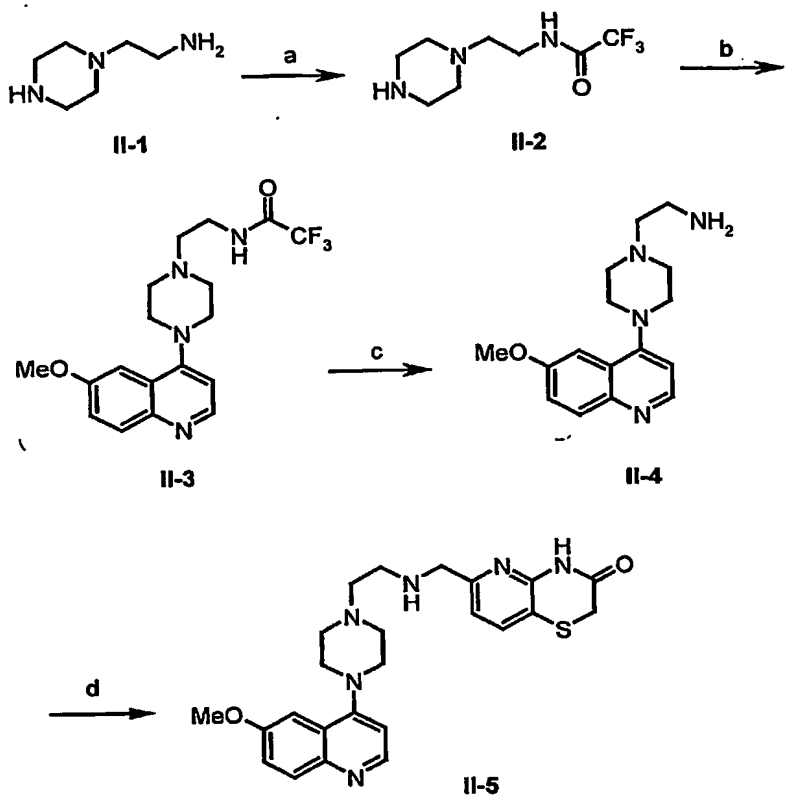


Reagents and Conditions: (a) $(Boc)_2O$, THF, RT; (b) PtO_2, 1N HCl, H_2 (1 atm), 12 h; (c) I-2, $EtN(i\text{-}Pr)_2$, DMF, 100 °C, 18 h; (d) TFA, CH_2Cl_2, RT; (e) 3-oxo-3,4-dihydro-2*H*-

pyrido[1,4]thiazine-6-carboxaldehyde, Na_2SO_4, EtOH, CH_2Cl_2, then $NaBH_4$.

Pyridine (**I-1**) is reacted with di-*tert*-butyl dicarbonate or a similar commercially available Boc-reagent to afford **I-2**. The use of protecting groups to mask reactive functionality is well-known to those of skill in the art, and other protecting groups are listed in standard reference volumes, such as Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Hydrogenation of the pyridine moiety under acidic conditions using an appropriate catalyst, such as Pt_2O, or others listed in standard reference books such as Rylander, "Hydrogenation Methods" (published by Academic Press) provides the piperidine **I-2**. Reaction of the piperidine **I-2** with an appropriately substituted pyridine electrophile **I-3** under thermal conditions provides compound **I-4**. See (*J. Med. Chem.* **2002**, *45*, 4975) for similar reaction examples. Removal of the Boc protecting group is carried out under standard acidic conditions to give the free amine **I-5**. The primary amine derivative is then converted to a secondary amine **I-6** by reaction with an aldehyde and a suitable reducing agent. For example, 2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamine is converted to an imine by reaction with an aldehyde in protic or aprotic solvents such as DMF, CH_2Cl_2, EtOH or CH_3CN. The imine is subsequently or simultaneously reacted with a suitable reducing agent such as $NaBH_4$, $NaBH(OAc)_3$ or $NaBH_3CN$ in solvent. Depending on whether acid neutralization is required, an added base, such as triethylamine (Et_3N), diisopropylethylamine ($(i\text{-}Pr)_2NEt$), or K_2CO_3, may be used. Many additional methods for reductive aminations are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience).

Scheme II

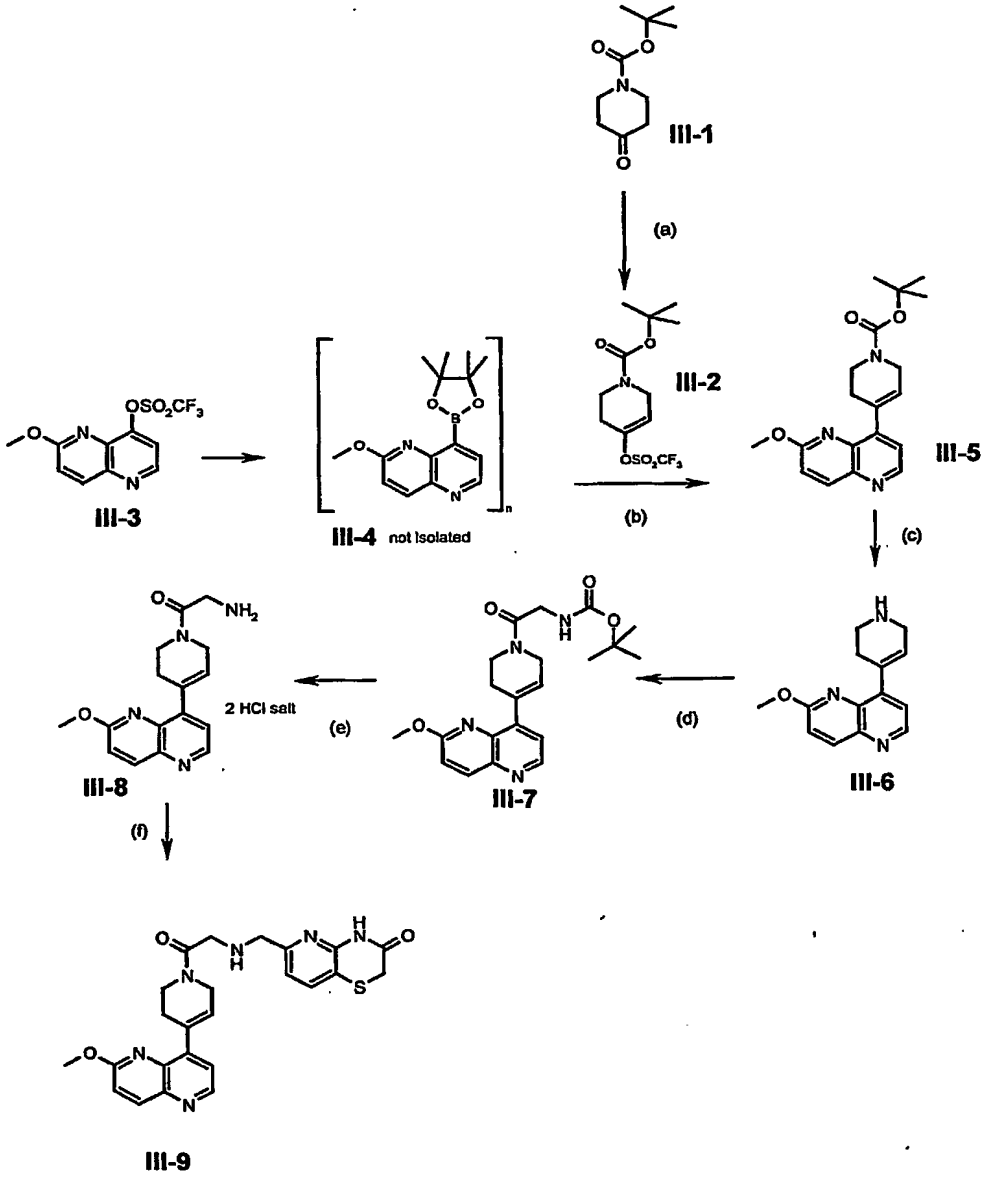


Reagents and Conditions: (a) Ethyl trifluoroacetate, THF, RT; (b) **II-3**, Et_3N, DMF, 100 °C, 18 h; (c) K_2CO_3, MeOH, H_2O, RT; (d) 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde, Na_2SO_4, EtOH, CH_2Cl_2, then $NaBH_4$.

Piperazine (**II-1**) is reacted with ethyl trifluoroacetate or a similar commercially available acylating reagent to afford **II-2**. The use of protecting groups to mask reactive functionality is well-known to those of skill in the art, and other protecting groups are listed in standard reference volumes, such as Greene, "Protective Groups in Organic Synthesis" (published by Wiley-Interscience). Reaction of the piperazine **II-2** with an appropriately substituted pyridine electrophile **II-3** under thermal conditions provides compound **II-3**. See (*J. Med. Chem.* **2002**, *45*, 4975) for similar reaction examples. Removal of the acyl protecting group is carried out under standard saponification conditions to give the free amine **II-4**. The primary amine derivative is then converted to a secondary amine **II-5** by reaction with an aldehyde and a suitable reducing agent. For example, 2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamine is converted to an imine by reaction with

an aldehyde in protic or aprotic solvents such as DMF, CH_2Cl_2, EtOH or CH_3CN. The imine is subsequently or simultaneously reacted with a suitable reducing agent such as $NaBH_4$, $NaBH(OAc)_3$ or $NaBH_3CN$ in solvent. Depending on whether acid neutralization is required, an added base, such as triethylamine (Et_3N), diisopropylethylamine ($(i\text{-}Pr)_2NEt$), or K_2CO_3, may be used. Many additional methods for reductive aminations are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience).

Scheme III



Reagents and Conditions: (a) LDA, -78°C, THF, then N-phenyltrifluromethanesulfonimide; (b) PDCl2 (dppf), KOAc, dppf, bispinacolatodiboron, 1,4-dioxane, 48h, 90°C, followed by PdCl2(dppf), potassium carbonate, 80°C 72h; (c) TFA, DCM, 1h, RT, then sodium bicarbonate; (d) N-boc-glycine, HATU, triethylamine, DMF, 18h, RT; (e) 4M HCL, 1,4-dioxane, $CHCl_3$, 15 min, RT; (f) 3-Oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carbaldehyde $NaCNBH_3$, MeOH, 18hr, RT.

Ketone (**III-1**) is reacted with LDA and then with N-phenyltrifluoromethanesulfonimide to give triflate (**I-2**) see (Synthesis 1991, 993). Triflate (**III-3**) is reacted under palladium catalysis to provide the crude intermediate (**III-4**) which is further reacted with (**III-2**) to give (**III-5**), see (Tetrahedron Letters 1997, 38 3447). Removal of the Boc protecting group is carried out under standard acidic conditions to give the free amine (**III-6**). The amine derivative is then coupled with N-Boc-glycine under standard HATU coupling conditions to give (**III-7**). Removal of the Boc protecting group is carried out under standard acidic conditions to give the free amine (**III-8**). The primary amine derivative is then converted to a secondary amine (**III-9**) by reaction with an aldehyde and a suitable reducing agent. For example, 2-Amino-1-[4-(6-methoxy-[1,5]naphthyridin-4-yl)-3,6-dihydro-2 H -pyridin-1-yl]-ethanone is converted to an imine by reaction with an aldehyde in protic or aprotic solvents such as DMF, CH_2Cl_2, EtOH or CH_3CN. The imine is subsequently or simultaneously reacted with a suitable reducing agent such as $NaBH_4$, $NaBH(OAc)_3$ or $NaBH_3CN$ in solvent. Depending on whether acid neutralization is required, an added base, such as triethylamine (Et_3N), diisopropylethylamine ($(i\text{-}Pr)_2NEt$), or K_2CO_3, may be used. Many additional methods for reductive aminations are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I - VI (published by Wiley-Interscience).

The antibacterial compounds according to the invention may be formulated for administration in any convenient way for use in human or veterinary medicine, by analogy with other antibacterials.

The pharmaceutical compositions of the invention include those in a form adapted for oral, topical or parenteral use and may be used for the treatment of bacterial infection in mammals including humans.

The composition may be formulated for administration by any route. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be

supplied to reconstitute the liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration. Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

No toxicological effects are indicated when a compound of formula (I) or a pharmaceutically acceptable derivative thereof is administered in the above-mentioned dosage range.

The compound of formula (I) may be the sole therapeutic agent in the compositions of the invention or a combination with other antibacterials. If the other antibacterial is a β-lactam then a β-lactamase inhibitor may also be employed.

Compounds of formula (I) are active against a wide range of organisms including both Gram-negative and Gram-positive organisms.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following examples illustrate the preparation of certain compounds of formula (I) and the activity of certain compounds of formula (I) against various bacterial organisms.

Abbreviations in the examples:

RT = room temperature

ES = Electrospray mass spec.

LCMS = Liquid chromatography mass spec.

APCI+ = Atmospheric pressure chemical ionisation mass spec.

Certain reagents are also abbreviated herein. DCC refers to dicyclohexylcarbodiimide, DMAP refers to dimethylaminopyridine, DIEA refers to diisopropylethyl amine, EDC refers to 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide,

hydrochloride. HOBt refers to 1-hydroxybenzotriazole, THF refers to tetrahydrofuran, DIEA refers to diisopropylethylamine, DEAD refers to diethyl azodicarboxylate, PPh_3 refers to triphenylphosphine, DIAD refers to diisopropyl azodicarboxylate, DME refers to dimethoxyethane, DMF refers to dimethylformamide, NBS refers to N-bromosuccinimide, Pd/C refers to a palladium on carbon catalyst, PPA refers to polyphosphoric acid, DPPA refers to diphenylphosphoryl azide, BOP refers to benzotriazol-1-yloxy-tris(dimethyl-amino)phosphonium hexafluorophosphate, HF refers to hydrofluoric acid, TEA refers to triethylamine, TFA refers to trifluoroacetic acid, PCC refers to pyridinium chlorochromate.

EXAMPLES AND EXPERIMENTALS

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 300 MHz, and chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (TMS). Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. $CDCl_3$ is deuteriochloroform, DMSO-d_6 is hexadeuteriodimethylsulfoxide, and CD_3OD or d_4-CH_3OH is tetradeuteriomethanol. Mass spectra were obtained using electrospray (ES) ionization techniques. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius. E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Flash chromatography was carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel. Analytical HPLC was performed on Beckman chromatography systems. Preparative HPLC was performed using Gilson chromatography systems. ODS refers to an octadecylsilyl derivatized silica gel chromatographic support. YMC ODS-AQ® is an ODS chromatographic support and is a registered trademark of YMC Co. Ltd., Kyoto, Japan. PRP-1® is a polymeric (styrene-divinylbenzene) chromatographic support, and is a registered trademark of Hamilton Co., Reno, Nevada. Celite® is a filter aid composed of acid-washed diatomaceous silica, and is a registered trademark of Manville Corp., Denver, Colorado.

Preparation 1

Preparation of (2-Piperidin-4-ylethyl) carbamic acid *tert*-butyl ester

a) (2-Pyridin-4-ylethyl) carbamic acid *tert*-butyl ester

To solution of 4-(2-aminoethyl)piperidine (10.0 g, 81.8 mmole) in THF at RT was added di-*tert*-butyl dicarbonate (17.9 g, 81.8 mmole). After 1 hr, the reaction solution was concentrated and purified on silica (EtOAc) to give the title compound as a colorless oil (18.0 g, 99%): LC-MS (ES) m/e 223 $(M + H)^+$.

b) (2-Piperidin-4-ylethyl) carbamic acid *tert*-butyl ester

To solution of (2-pyridin-4-ylethyl) carbamic acid *tert*-butyl ester (18.0 g, 81.0 mmole) in MeOH (250 mL) at RT was added 6N HCl (13.6 mL) and PtO_2 (900 mg). After 18 hr under a balloon of H_2 with vigorous stirring, the reaction solution was filtered through Celite® and concentrated under vacuum. The residue was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4 and concentrated to give the title compound as a colorless viscous oil (17.6 g, 95%): LC-MS (ES) m/e 229 $(M + H)^+$.

Preparation 2

Preparation of 1,1,1-trifluoro-*N*-(2-piperazin-1-ylethyl)acetamide

To solution of 1-(2-aminoethyl)piperazine (8.0 g, 61.9 mmole) in THF (100 mL) at 0 °C was added ethyl trifluoroacetate (7.38 mL, 61.9 mmole). The reaction solution was allowed to warm to RT over 2 hr and then was concentrated to give the title compound as a pale yellow solid (13.9 g, 99%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 3.40 (q, J = 5 Hz, 2H), 2.88 (t, J = 5 and 4.8 Hz, 4 H), 2.53 (t, J = 6 and 5.8 Hz, 2H), 2.44 (s, 4H), and 1.86 (s, 1H). LC-MS (ES) m/e 226 $(M + H)^+$.

Example 1

Preparation of 6-({2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

a) {2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester

To a solution of (2-piperidin-4-ylethyl) carbamic acid *tert*-butyl ester (2.1 g, 9.2 mmole) in DMF (5 mL) at RT was added 4-bromo-6-methoxyquinoline (2.0 g, 8.4 mmole) and Et_3N (0.86 g, 8.37 mmole). After 18 hour at 100 °C, the reaction solution was concentrated under vacuum and purified by flash chromatography on silica gel ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to afford the title compound as a tan solid (2.39 g, 74%): ^1H NMR (400 MHz, $CDCl_3$) 8.61 (m, 1H), 8.03 (m, 1H), 7.37 (m, 1H), 7.22 (m, 1H), 6.85 (m, 1H), 4.57 (br s, 1H), 3.98 (s, 3H), 3.72 (m, 1H), 3.25 (m, 1H), 2.99 (app

s, 2H), 2.90 (app s, 2H), 2.80 (m, 2H), 1.95 (m, 1H), 1.65-1.50 (m, 4H), 1.48 (s, 9H). LC-MS (ES) m/e 386 $(M + H)^+$

b) 2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamine

To a solution of {2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester (2.39 g, 6.20 mmole) in CH_2Cl_2 at RT was added TFA (1:1, v/v). After 2 hrs, the solution was concentrated to dryness under vacuum and the residue redissolved in CH_2Cl_2/ MeOH (9:1, v/v). The solution was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under vacuum to give the title compound (1.62 g, 92%) as a waxy yellow solid: LC-MS (ES) m/e 286 $(M + H)^+$.

c) 6-({2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

To a solution of 2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamine (0.15 g, 0.53 mmole) in CH_2Cl_2 (25 mL) and EtOH (25 mL) was added Na_2SO_4 (50 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.11 g, 0.55 mmole). After 12 hr at RT, $NaBH_4$ (21 mg, 0.55 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (0.21 g, 86 %) as an off-white solid: ^1H NMR (400 MHz, d_4-MeOH) 8.47 (d, J = 6.5 Hz, 1H), 7.91 (d, J = 9.3 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.61 (d, J = 9.3 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.17 (m, 2H), 4.35 (s, 2H), 4.14 (m, 2H), 4.01 (s, 3H), 3.58 (s, 2H), 3.33 (m, 1H), 3.27 (m, 2H), 2.05 (m, 2H), 1.84 (m, 4H), 1.63 (m, 2H). LC-MS (ES) m/e 464 $(M + H)^+$.

Example 2

Preparation of 6-({2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

According to the procedure of Example 1c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (0.10 g, 0.55 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.19 g, 81 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, d_4-MeOH) 8.46 (d, J = 6.5 Hz, 1H), 7.93 (d, J = 9.3 Hz, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.40 (m, 2H), 7.21 (d, J = 6.6 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 4.72 (s, 2H), 4.29 (s, 2H), 4.23 (m, 2H), 4.02 (s, 3H),

3.45 (m, 2H), 3.21 (m, 2H), 2.06 (m, 2H), 1.86 (m, 4H), 1.66 (m, 2H). LC-MS (ES) m/e 448 $(M + H)^+$.

Example 3

Preparation of (2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-{2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}amine

According to the procedure of Example 1c, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (0.25 g, 1.51 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.55 g, 84 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, d_4-MeOH) 8.46 (m, 2H), 7.92 (d, J = 9.3 Hz, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.52 (s, 1H), 7.40 (d, J = 2.5 Hz, 1H), 7.21 (d, J = 6.9 Hz, 1H), 4.60 (m, 2H), 4.50 (m, 2H), 4.49 (s, 2H), 4.26 (m, 2H), 4.02 (s, 3H), 3.45 (m, 2H), 3.33 (s, 2H), 3.30 (m, 2H), 2.08 (m, 2H), 1.95 (m, 1H), 1.86 (m, 2H), 1.66 (m, 2H). LC-MS (ES) m/e 435 $(M + H)^+$.

Example 4

Preparation of 6-({2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

a) {2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester

To a solution of (2-piperidin-4-ylethyl) carbamic acid *tert*-butyl ester (0.81 g, 3.57 mmole) in DMF (5 mL) at RT was added 1,1,1-trifluoromethane sulfonic acid 6-methoxy[1,5]naphthyridin-4-yl ester (1.0 g, 3.24 mmole) and Et_3N (0.33 g, 3.24 mmole). After 18 hour at 100 °C, the reaction solution was concentrated under vacuum and purified by flash chromatography on silica gel ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to afford the title compound as a tan solid (1.19 g, 95%): ^1H NMR (400 MHz, $CDCl_3$) 8.51 (d, J = 5.3 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.09 (d, J = 9.0 Hz, 1H), 6.85 (d, J = 5.3 Hz, 1H), 4.55 (br s, 1H), 4.36 (m, 2H), 4.06 (s, 3H), 3.25 (m, 2H), 2.90 (m, 2H), 1.92 (m, 2H), 1.57 (m, 4H), 1.47 (s, 9H). LC-MS (ES) m/e 387 $(M + H)^+$.

b) 2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamine

To a solution of {2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester (1.19 g, 3.08 mmole) in CH_2Cl_2 at RT was added TFA (1:1, v/v). After 2 hrs, the solution was concentrated to dryness under vacuum and the residue redissolved in CH_2Cl_2/ MeOH (9:1, v/v). The solution was washed with saturated

aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under vacuum to give the title compound (0.79 g, 90%) as a waxy yellow solid: LC-MS (ES) m/e 287 $(M + H)^+$.

c) 6-({2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

To a solution of 2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamine (1.25 g, 4.37 mmole) in CH_2Cl_2 (70 mL) and EtOH (50 mL) was added Na_2SO_4 (100 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.89 g, 4.59 mmole). After 12 hr at RT, $NaBH_4$ (0.17 mg, 4.59 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (1.58 g, 78 %) as an off-white solid: ^1H NMR (400 MHz, $CDCl_3$) 8.51 (d, J = 5.4 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.09 (d, J = 9.0 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.85 (d, J = 5.4 Hz, 2H), 4.37 (m, 2H), 4.06 (s, 3H), 3.94 (s, 2H), 3.50 (s, 2H), 2.94 (m, 4H), 1.61-1.92 (m, 7H). LC-MS (ES) m/e 465 $(M + H)^+$.

Example 5

Preparation of 6-({2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

According to the procedure of Example 4c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (0.82 g, 4.59 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (1.37 g, 70 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, $CDCl_3$) 8.53 (d, J = 5.4 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 5.4 Hz, 2H), 4.67 (s, 2H), 4.35 (m, 2H), 4.06 (s, 3H), 3.87 (s, 2H), 2.88 (m, 2H), 2.76 (m, 2H), 1.87 (m, 2H), 1.64 (m, 5H). LC-MS (ES) m/e 449 $(M + H)^+$.

Example 6

Preparation of (2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-{2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}amine

According to the procedure of Example 4c, except substituting 2,3-dihydro[1,4]dioxino[2,3-c]pyridine-7-carboxaldehyde (0.25 g, 1.51 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (1.19 g, 79 %)

was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, $CDCl_3$) 8.33 (d, J = 6.3 Hz, 1H), 8.15 (m, 2H), 7.35 (d, J = 9.1 Hz, 1H), 7.14 (d, J = 6.7 Hz, 1H), 7.03 (s, 1H), 4.96 (m, 2H), 4.39 (m, 2H), 4.26 (m, 2H), 4.24 (s, 2H), 4.08 (s, 3H), 3.31 (m, 2H), 3.21 (s, 2H), 2.05 (m, 2H), 1.91 (m, 1H), 1.79 (m, 2H), 1.61 (m, 2H). LC-MS (ES) m/e 436 $(M + H)^+$.

Example 7

Preparation of 6-({2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one a) {2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester

To a solution of (2-piperidin-4-ylethyl) carbamic acid *tert*-butyl ester (1.20 g, 5.27 mmole) in DMF (5 mL) at RT was added 1,1,1-trifluoromethane sulfonic acid 3-chloro-6-methoxy[1,5]quinolin-4-yl ester (1.50 g, 4.39 mmole) and Et_3N (0.45 g, 4.39 mmole). After 18 hour at 100 °C, the reaction solution was concentrated under vacuum and purified by flash chromatography on silica gel (EtOAc) to afford the title compound as a tan solid (1.20 g, 65%): ^1H NMR (400 MHz, $CDCl_3$) 8.55 (m, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.45 (m, 1H), 7.33 (m, 1H), 4.51 (br s, 1H), 3.97 (s, 3H), 3.46 (m, 2H), 3.33 (m, 3H), 3.25 (m, 2H), 1.87 (m, 2H), 1.60 (m, 4H), 1.48 (s, 9H). LC-MS (ES) m/e 420 $(M + H)^+$.

b) 2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamine

To a solution of {2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester (1.19 g, 3.08 mmole) in CH_2Cl_2 (50 mL) at RT was added TFA (1:1, v/v). After 2 hrs, the solution was concentrated to dryness under vacuum and the residue redissolved in CH_2Cl_2/ MeOH (9:1, v/v). The solution was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under vacuum to give the title compound (0.82 g, 90%) as a tan solid: LC-MS (ES) m/e 320 $(M + H)^+$.

c) 6-({2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

To a solution of 2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamine (0.40 g, 1.26 mmole) in CH_2Cl_2 (75 mL) and EtOH (50 mL) was added Na_2SO_4 (100 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.26 g, 1.32 mmole). After 12 hr at RT, $NaBH_4$ (21 mg, 0.55 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the

contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (0.50 g, 80 %) as an off-white solid: ^1H NMR (400 MHz, $CDCl_3$) 8.54 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.46 (m, 1H), 7.32 (m, 1H), 7.05 (d, J = 7.8 Hz, 1H), 4.01 (s, 2H), 3.97 (s, 3H), 3.50 (s, 2H), 3.42 (m, 2H), 3.26 (m, 2H), 2.92 (m, 2H), 1.55-1.80 (m, 7H). LC-MS (ES) m/e 482 $(M + H)^+$.

Example 8

Preparation of 6-({2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one According to the procedure of Example 7c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (0.23 g, 1.32 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.47 g, 78 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, $CDCl_3$) 8.53 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.46 (m, 1H), 7.28 (m, 2H), 7.06 (d, J = 8.1 Hz, 1H), 4.68 (s, 2H), 4.04 (s, 2H), 3.96 (s, 3H), 3.46 (m, 2H), 3.25 (m, 2H), 2.94 (m, 2H), 1.52-1.84 (m, 7H). LC-MS (ES) m/e 498 $(M + H)^+$.

Example 9

Preparation of {2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine

According to the procedure of Example 7c, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (0.14 g, 0.83 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.32 g, 83 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, CD_3OD) 8.83 (s, 1H), 8.54 (s, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.70 (m, 1H), 7.64 (s, 1H), 7.53 (s, 1H), 4.65 (m, 3H), 4.53 (m, 3H), 4.10 (m, 2H), 4.05 (s, 3H), 3.77 (m, 2H), 3.32 (m, 2H), 2.10 (m, 2H), 1.87 (m, 2H), 1.66 (m, 2H). LC-MS (ES) m/e 469 $(M)^+$.

Example 10

Preparation of 6-({2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one a) {2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester

To a solution of (2-piperidin-4-ylethyl) carbamic acid *tert*-butyl ester (1.83 g, 8.02 mmole) in DMF (10 mL) at RT was added 1,1,1-trifluoromethane sulfonic acid 3-chloro-6-methoxy[1,5]naphthyridin-4-yl ester (2.50 g, 7.29 mmole) and Et_3N (0.74 g, 7.30 mmole). After 18 hour at 100 °C, the reaction solution was concentrated under vacuum and purified by flash chromatography on silica gel (EtOAc/hexanes, 1:1) to afford the title compound as a tan solid (2.0 g, 65%): ^1H NMR (400 MHz, $CDCl_3$) 8.55 (s, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 4.52 (br s, 1H), 4.05 (s, 3H), 3.78 (m, 2H), 3.50 (m, 2H), 3.25 (m, 2H), 1.84 (m, 2H), 1.48-1.54 (m, 5H). LC-MS (ES) m/e 421 $(M + H)^+$.

b) 2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamine

To a solution of {2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}carbamic acid *tert*-butyl ester (2.0 g, 4.76 mmole) in CH_2Cl_2 (50 mL) at RT was added TFA (1:1, v/v). After 2 hrs, the solution was concentrated to dryness under vacuum and the residue redissolved in CH_2Cl_2/ MeOH (9:1, v/v). The solution was washed with saturated aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and concentrated under vacuum to give the title compound (1.29 g, 85%) as a tan viscous solid: LC-MS (ES) m/e 321 $(M + H)^+$.

c) 6-({2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

To a solution of 2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamine (0.74 g, 2.33 mmole) in CH_2Cl_2 (100 mL) and EtOH (50mL) was added Na_2SO_4 (100 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.47 g, 2.45 mmole). After 12 hr at RT, $NaBH_4$ (93 mg, 2.45 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (0.90 g, 77 %) as an off-white solid: ^1H NMR (400 MHz,$CDCl_3$) 8.54 (s, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 4.70 (s, 1H), 4.04 (s, 3H), 3.98 (s, 2H), 3.78 (m, 2H), 3.49 (m, 4H), 2.88 (m, 2H), 1.56-1.79 (m, 6H). LC-MS (ES) m/e 499 $(M + H)^+$.

Example 11

Preparation of 6-({2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one According to the procedure of

Example 10c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (0.44 g, 2.45 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (1.0 g, 89 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz,$CDCl_3$) 8.55 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 4.68 (m, 3H), 4.04 (s, 3H), 3.91 (s, 2H), 3.76 (m, 2H), 3.50 (m, 2H), 2.80 (m, 2H), 1.81 (m, 2H), 1.67 (m, 2H), 1.54 (m, 2H). LC-MS (ES) m/e 483 $(M + H)^+$.

Example 12

Preparation of {2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine According to the procedure of Example 10c, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (0.15 g, 0.93 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.35 g, 80 %) was prepared as an off-white viscous oil following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, CD_3OD) 8.79 (s, 1H), 8.55 (s, 1H), 8.25 (d, J = 9.2 Hz, 1H), 7.69 (s, 1H), 7.46 (d, J = 9.2 Hz, 1H), 4.67 (m, 2H), 4.54 (m, 6H), 4.14 (s, 3H), 3.72 (m, 2H), 3.32 (m, 2H), 2.06 (m, 2H), 1.87 (m, 2H), 1.69 (m, 2H). LC-MS (ES) m/e 470 $(M)^+$.

Example 13

Preparation of 6-({2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-b][1,4]oxazin-3-one

(a) 2,2,2-trifluoro-N-{2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}acetamide

To solution of 1,1,1-trifluoro-*N*-(2-piperazin-1-ylethyl)acetamide (2.3 g, 10.0 mmole) in DMF (5 mL) at RT was added 4-bromo-6-methoxyquinoline (2.0 g, 8.4 mmole) and triethylamine (0.86 mL, 8.4 mmole). After 18 hr at 100 °C, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as an off-white solid (2.32 g, 73 %): LC-MS (ES) m/e 383 $(M + H)^+$.

(b) 2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamine

To solution of 2,2,2-trifluoro-N-{2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}acetamide (1.11 g, 2.9 mmole) in methanol (50 mL) at RT was added K_2CO_3 (2.0 g, 14.5 mmole) and H_2O (25 mL). After 18 hr at RT, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as a thick oil (0.75 g, 90 %): ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 5 Hz, 1H), 7.99 (d, J = 9 Hz, 1H), 7.36 (d, J = 2.8 Hz, 1H), 7.32 (m, 1H), 6.88 (d, J = 5 Hz, 1H), 3.95 (s, 3H), 3.25 (s, 4H), 2.89 (t, J = 6 Hz, 2H), 2.80 (s, 4H), 2.58 (t, J = 6 Hz, 2H), and 1.62 (s, 2H).

(c) 6-({2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-b][1,4]oxazin-3-one

To a solution of 2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamine (0.35 g, 1.22 mmole) in CH_2Cl_2 (25 mL) and EtOH (25 mL) was added Na_2SO_4 (50 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]oxazine-6-carboxaldehyde (0.22g, 1.22 mmole). After 12 hr at RT, $NaBH_4$ (46 mg, 1.22 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (0.27 g, 50 %) as an off-white solid: ^1H NMR (400 MHz, d_4-MeOH) 8.71 (d, J= 6.3 Hz, 1H), 8.03 (d, J = 9 Hz, 1H), 7.75 (dd, J = 9 and 2.8 Hz, 1H), 7.42 (m, 3H), 7.15 (d, J = 8 Hz, 1H), 4.73 (s, 2H), 4.40 (s, 2H), and 3.97 (m, 15H). LC-MS (ES) m/e 449 (M + H)$^+$.

Example 14

Preparation of 6-({2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-b][1,4]thiazin-3-one

According to the procedure of Example 13c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde (0.24 g, 1.26mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde, the title compound (0.22 g, 45 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, d_4-CH_3OH) 8.68 (d, J = 6.6 Hz, 1H), 8.02 (d, J = 9.3 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 9.3 Hz, 1H), 7.43 (m, 2H), 7.18 (d, J = 7.8 Hz, 1H), 4.46 (s, 2H), and 3.83 (m, 16H). LC-MS (ES) m/e 465 (M + H)$^+$.

Example 15

Preparation of (2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)-{2-[4-(6-methoxyquinolin-4-yl)piperizin-1-yl]ethyl}amine

According to the procedure of Example 13c, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (0.21 g, 1.26 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde, the title compound (86 mg, 25 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, d_4-CH_3OH) 8.59 (d, J = 7.0 Hz, 1H), 8.29 (s, 1H), 7.91 (d, J = 9.4 Hz, 1H), 7.63 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 7.0 Hz, 1H), 4.47 (s, 2H), 4.35 (m, 4H), 4.01 (m,.4H), 3.96 (s, 3H), 3.67 (m, 4H) and 3.58 (m, 4H). LC-MS (ES) m/e 436 $(M + H)^+$.

Example 16

Preparation of 6-({2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-b][1,4]thiazin-3-one (SB-829797)

(a) 2,2,2-trifluoro-N-{2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethyl}acetamide

To solution of 1,1,1-trifluoro-*N*-(2-piperazin-1-ylethyl)acetamide (2.2 g, 9.73 mmole) in DMF (5 mL) at RT was added 1 1,1-trifluoromethanesulfonic acid 6-methoxy[1,5]naphthyridin-4-yl ester (3.0 g, 9.73 mmole) and triethylamine (1.63 mL, 11.68 mmole). After 18 hr at 100 °C, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as an off-white solid (2.70 g, 72 %): LC-MS (ES) m/e 384 $(M + H)^+$.

(b) 2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamine

To solution of 2,2,2-trifluoro-N-{2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}acetamide (2.70 g, 7.0 mmole) in methanol (100 mL) at RT was added K_2CO_3 (4.86 g, 35.2 mmole) and H_2O (25 mL). After 18 hr at RT, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as a thick oil (1.75 g, 86 %): LC-MS (ES) m/e 288 $(M + H)^+$.

(c) 6-({2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

To a solution of 2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamine (1.0 g, 3.48 mmole) in CH_2Cl_2 (50 mL) and EtOH (50 mL) was added Na_2SO_4 (50 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.68 g, 3.48 mmole). After 12 hr at RT, $NaBH_4$ (132 mg, 3.48 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (0.90 g, 50 %) as an off-white solid: ^1H NMR (400 MHz, d_4-MeOH) 8.53 (d, J = 7 Hz, 1H), 8.27 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 9.2 Hz, 1H), 7.39 (d, J = 7 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 4.46 (s, 2H), 4.12 (s, 3H), 3.80 (m, 8 H), and 3.59 (s, 2H). LC-MS (ES) m/e 466 (M + H)$^+$.

Example 17

Preparation of 6-({2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-b][1,4]oxazin-3-one

According to the procedure of Example 16c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (0.50 g, 2.82 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.75 g, 60 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, d_4-CH_3OH) 8.49 (d, J = 7.0 Hz, 1H), 8.24 (d, J = 9.2 Hz, 1H), 7.49 (d, J = 9.2 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 7 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 4.73 (s, 2H), 4.38 (s, 2H), 4.11 (s, 3H), and 3.59 (m, 8H). LC-MS (ES) m/e 450 (M + H)$^+$.

Example 18

Preparation of (2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-{2-[4-(6-methoxy[1,5]naphthyridin-4-yl)piperazin-1-yl]ethyl}amine

According to the procedure of Example 16c, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (0.08 g, 0.47 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.10 g, 50 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, d_4-CH_3OH) 8.52 (d, J = 7.2 Hz, 1H), 8.38 (s, 1H), 7.27 (d, J = 9.2 Hz, 1H), 7.50 (d, J = 9.2 Hz, 1H), 7.42 (s, 1H),

7.38 (d, J = 7.2 Hz, 1H), 4.73 (s, 4H), 4.56 (m, 2H), 4.46 (m, 2H), 4.43 (s, 2H), 4.12 (s, 3H), 3.75 (m, 4H), and 3.65 (s, 4H). LC-MS (ES) m/e 437 $(M + H)^+$.

Example 19

Preparation of 6-({2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

(a) 2,2,2-trifluoro-N-{2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}acetamide

To solution of 1,1,1-trifluoro-*N*-(2-piperazin-1-ylethyl)acetamide (2.01 g, 8.78 mmole) in DMF (5 mL) at RT was added 1 1,1-trifluoromethanesulfonic acid 3-chloro-6-methoxy[1,5]quinolin-4-yl ester (3.0 g, 8.78 mmole) and triethylamine (1.50mL, 10.5 mmole). After 18 hr at 100 °C, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as an off-white solid (2.40 g, 66 %): LC-MS (ES) m/e 417 $(M + H)^+$.

(b) 2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamine

To solution of 2,2,2-trifluoro-N-{2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}acetamide (2.40 g, 5.75 mmole) in methanol (100 mL) at RT was added K_2CO_3 (4.10 g, 30.0 mmole) and H_2O (25 mL). After 18 hr at RT, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as a waxy yellow solid (1.40 g, x %): LC-MS (ES) m/e 321 $(M + H)^+$.

(c) 6-({2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

To a solution of 2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamine (0.56 g, 1.74 mmole) in CH_2Cl_2 (50 mL) and EtOH (50 mL) was added Na_2SO_4 (50 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.34 g, 1.74 mmole). After 12 hr at RT, $NaBH_4$ (66 mg, 1.74 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (0.49 g, 57 %) as an off-white solid: ^1H NMR (400 MHz, CD_3OD) 9.04 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.52

(m, 1H), 7.18 (d, J = 7.8 Hz, 1H), 4.48 (s, 2H), 4.25 (m, 4H), 4.13 (s, 3H), 3.84 (m, 4H), 3.75 (m, 2H), 3.60 (m, 2H), 3.37 (m, 2H). LC-MS (ES) m/e 499 $(M)^+$.

Example 20

Preparation of 6-({2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

According to the procedure of Example 19c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (0.28 g, 1.56 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.56 g, 70 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, DMSO-d_6) 10.10 (br s, 1H), 8.89 (s, 1H), 8.14 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 9.2 Hz, 1H), 7.45 (m, 2H), 7.34 (d, J = 8.1 Hz, 1H), 4.70 (s, 2H), 4.23 (m, 2H), 4.04 (s, 3H), 3.85-3.60 (m, 12H). LC-MS (ES) m/e 483 $(M)^+$.

Example 21

Preparation of {2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine

According to the procedure of Example 19c, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (0.10 g, 0.62 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.25 g, 86 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, DMSO-d_6) 8.80 (s, 1H), 8.36 (s, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.43 (m, 2H), 4.48 (s, 2H), 4.39 (s, 2H), 4.35 (m, 2H), 4.02 (s, 3H), 3.83-3.61 (m, 12H). LC-MS (ES) m/e 470 $(M)^+$.

Example 22

Preparation of 6-({2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

(a) 2,2,2-trifluoro-N-{2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethyl}acetamide

To solution of 1,1,1-trifluoro-*N*-(2-piperazin-1-ylethyl)acetamide (2.10 g, 9.31 mmole) in DMF (5 mL) at RT was added 1 1,1-trifluoromethanesulfonic acid 3-chloro-6-methoxy[1,5]quinolin-4-yl ester (3.19 g, 9.31 mmole) and triethylamine (1.30 mL, 9.31

mmole). After 18 hr at 100 °C, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as an off-white solid (2.61 g, 67 %): LC-MS (ES) m/e 418 $(M + H)^+$.

(b) 2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamine

To solution of 2,2,2-trifluoro-N-{2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethyl}acetamide (2.61 g, 6.24 mmole) in methanol (100 mL) at RT was added K_2CO_3 (4.31 g, 31.2 mmole) and H_2O (25 mL). After 18 hr at RT, the reaction solution was concentrated under vacuum and purified on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH) to give the title compound as a light yellow solid (2.0 g, 99 %): LC-MS (ES) m/e 322 $(M + H)^+$.

(c) 6-({2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one

To a solution of 2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamine (1.0 g, 3.11 mmole) in CH_2Cl_2 (50 mL) and EtOH (50 mL) was added Na_2SO_4 (50 mg) and 3-oxo-3,4-dihydro-2*H*-pyrido[1,4]thiazine-6-carboxaldehyde (0.61 g, 3.11mmole). After 12 hr at RT, $NaBH_4$ (120 mg, 3.11 mmole) was added and the reaction solution was allowed to stir overnight. Silica gel (~5 g) was added to the reaction solution and the contents were concentrated under vacuum. The silica-adsorbed reaction contents were added directly to a silica gel column ($CHCl_3$/MeOH containing 5% NH_4OH, 9:1) to give the title compound (0.82 g, 53 %) as an off-white solid: ^1H NMR (400 MHz, DMSO-d_6) 10.10 (br s, 1H), 8.89 (s, 1H), 8.42 (d, J = 9.2 Hz, 1H), 7.91(d, J = 7.0 Hz, 1H), 7.42 (d, J = 9.2 Hz, 2H), 7.35 (d, J = 7.0 Hz, 1H), 4.28 (s, 2H), 4.12 (s, 4H), 4.05 (s, 3H), 3.81 (m, 2H), 3.73 (m, 4H), 3.61 (s, 2H), 3.42 (m, 2H). LC-MS (ES) m/e 500 $(M + H)^+$.

Example 23

Preparation of 6-({2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one

According to the procedure of Example 22c, except substituting 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine-6-carboxaldehyde (0.56 g, 3.11 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.98 g, 65 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, DMSO-d_6) 9.84 (br s, 1H), 8.70 (s, 1H), 8.24 (d, J = 9.2 Hz, 1H), 7.37 (d, J = 9.2 Hz, 1H), 7.25 (m, 2H), 4.61 (s,

2H), 4.13 (s, 2H), 4.05 (m, 2H); 3.95 (s, 3H), 3.89 (m, 2H), 3.70 (m, 2H), 3.58 (m, 4H), 3.28 (m, 2H). LC-MS (ES) m/e 484 $(M + H)^+$.

Example 24

Preparation of (2,3-dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-{2-[4-(3-chloro-6-methoxy[1,5]naphthyridin-4-yl)piperazin-1-yl]ethyl}amine

According to the procedure of Example 22c, except substituting 2,3-dihydro[1,4]dioxino[2,3-*c*]pyridine-7-carboxaldehyde (0.23 g, 1.40 mmole) for 3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazine-6-carboxaldehyde, the title compound (0.54g, 82 %) was prepared as an off-white solid following flash chromatography on silica gel ($CHCl_3$/MeOH, 9:1, containing 5% NH_4OH): ^1H NMR (400 MHz, DMSO-d_6) 8.81 (s, 1H), 8.33 (m, 2H), 7.34 (m, 2H), 4.45 (s, 2H), 4.38 (s, 2H), 4.28 (m, 2H), 4.05 (s, 3H), 4.02 (m 2H), 3.66 (m, 2H), 3.58 (m, 2H), 3.45-3.33 (m, 6H). LC-MS (ES) m/e 469 $(M)^+$.

Example 25

Preparation of 6-({2-[4-(6-Methoxy-[1,5]naphthyridin-4-yl)-3,6-dihydro-2 H -pyridin-1-yl]-2-oxo-ethylamino}-methyl) -4 H -pyrido[3,2-b][1,4]thiazin-3-one

(a) 4-Trifluoromethanesulfonyloxy-3,6-dihydro-2 H -pyridine-1-carboxylic acid tert -butyl ester

According to the procedure of Wustrow and Wise (Synthesis 1991, 993) to a solution of N-Boc-piperidone (7.99 g) in THF (50 mL) at –78°C was added LDA (2M in THF) and the solution was stirred for 30 min. N-phenyltrifluoromethanesulfonimide (3.08 g) was then added and the reaction warmed to room temperature, treated with water (100 mL). The reaction was then extracted with dichloromethane (2 x 200 mL) and the organic fraction dried ($MgSO_4$). The product was purified by column chromatography (9:1 petrol:ethyl acetate) to give the product as a colourless solid (10.64 g).

MS (+ve ion electrospray) m/z 332 (MH^+).

(b) 4-(6-Methoxy-[1,5]naphthyridin-4-yl)-3,6-dihydro-2 H -pyridine-1-carboxylic acid tert -butyl ester

According to the procedure of Ishiyama, Itoh, Kitano and Miyaura (Tetrahedron Letters 1997, 38 3447) to a solution of 1,1,1-trifluoro-methanesulfonic acid 6-methoxy-[1,5]naphthyridin-4-yl ester (4.15 g) in 1,4-dioxane (60 mL) was added $PdCl_2$(dppf) (296mg), KOAc (3.95 g), dppf (221 mg) and bispinacolatodiboron (3.76 g). This mixture was heated at 90°C for 24h. After this time another 592 mg of $PdCl_2$(dppf) was added and

the reaction was stirred at 90°C for a further 24h. The reaction mixture was then treated with water (100 mL) and extracted with dichloromethane (2 x 200mL) and the organic fraction dried ($MgSO_4$) and evaporated *in vacuo*. To this crude material was added triflate (a), potassium carbonate, $PdCl_2$(dppf) (591 mg) and DMF (100 mL) and the mixture was stirred at 80°C for 72h. The reaction mixture was then treated with water (100 mL) and extracted with dichloromethane (3 x 100 mL) and the organic fraction dried ($MgSO_4$) and purified by by column chromatography (4:1 petrol:ethyl acetate) to give the product as a yellow solid (2.53 g).
MS (+ve ion electrospray) m/z 342 (MH^+).

(c) 2-Methoxy-8-(1,2,3,6-tetrahydro-pyridin-4-yl)-[1,5]naphthyridine
To a solution of compound (b) (2.54 g) in DCM (50 mL) was added TFA (10 mL) and the reaction was stirred at room temperature for 1h before being evaporated in vacuo and basified with saturated sodium bicarbonate (10 mL) and extracted with 9:1 MeOH:DCM (3 x 100 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated *in vacuo* to give (c) as a yellow solid (1.64 g).
MS (+ve ion electrospray) m/z 242 (MH^+).

(d) {2-[4-(6-Methoxy-[1,5]naphthyridin-4-yl)-3,6-dihydro-2 H -pyridin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester
To a solution of N-Boc-glycine (239 mg) in DMF (10ml) was added triethylamine (0.68 mL) was added HATU (517 mg) and the solution was stirred for 10 min. Compound (c) (262 mg) was then added and the solution was stirred for 18h. The reaction mixture was then treated with water (20 mL) and extracted with dichloromethane (2 x 50 mL) and the organic fraction dried ($MgSO_4$) and purified by by column chromatography (1:1 petrol:ethyl acetate) to give (d) as a yellow solid (416 mg).
MS (+ve ion electrospray) m/z 399 (MH^+).

(e) 2-Amino-1-[4-(6-methoxy-[1,5]naphthyridin-4-yl)-3,6-dihydro-2 H -pyridin-1-yl]-ethanone dihydrochloride
To a solution of (d) (410 mg) in methanol (5 mL) was added 4M HCl in dioxane (10 mL) and the solution was stirred at room temperature for 15 min. The reaction mixture was then evaporated in vacuo to give (e) (297 mg) as a yellow solid.
MS (+ve ion electrospray) m/z 299 (MH^+).

(f) Title compound

To a mixture of (e) (182 mg) in methanol (3 mL) and molecular sieves was added sodium cyanoborohydride (25 mg) and 3-Oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]thiazine-6-carbaldehyde (95 mg) and the resultant micture was stirred at room temperature for 18h. The reaction mixture was then treated with water (10 mL) and extracted with 9:1 dichloromethane:methanol (3 x 50 mL) and the organic fraction dried ($MgSO_4$) and purified by by column chromatography (9:1 dichloromethane:methanol) to give (f) as a yellow solid (71 mg).

^1H NMR □H (DMSO, 400MHz), 10.90 (s, 1H), 8.74 (d, *J* = 4.5 Hz, 1H), 8.26 (d, *J* = 9.0 Hz, 1H), 7.73-7.77 (m, 1H), 7.52-7.54 (m, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 1H), 6.35 (br s, 1H), 4.20 (s, 2H), 3.97 (s, 3H), 3.77 (s, 2H), 3.63-3.66 (m, 1H), 3.52-3.55 (m, 6H), 2.78-2.84 (m, 2H).

MS (ES) *m/z* 477 $(M + H)^+$.

This material was converted to the dihydrochloride by dissolving in chloroform and adding 2 equivalents of 1M HCl/ether then evaporating to dryness.

Antimicrobial Activity Assay:

Whole-cell antimicrobial activity was determined by broth microdilution using the National Committee for Clinical Laboratory Standards (NCCLS) recommended procedure, Document M7-A4, "Methods for Dilution Susceptibility Tests for Bacteria that Grow Aerobically". The compounds were tested in serial two-fold dilutions ranging from 0.016 to 16 mcg/mL. Compounds were evaluated against a panel of Gram-(+) organisms, including *Staphylococcus aureus* WCUH29, *Staphylococcus epidermidis* CL7, *Streptococcus pneumoniae* 1629, *Streptococcus pyogenes* CN 10, and *Enterococcus faecalis* 2. In addition, compounds were evaluated against a panel of Gram-(-) strains including *Haemophilus influenzae* NEMC1, *E. coli* 7623, and *Moraxella catarrhalis* Ravasio. The minimum inhibitory concentration (MIC) was determined as the lowest concentration of compound that inhibited visible growth. A mirror reader was used to assist in determining the MIC endpoint.

One skilled in the art would consider any compound with a MIC of less than 16 μg/mL to be a potential lead compound. Preferably, the compounds used in the antimicrobial assays of the present invention have a MIC value of less than 8μg/mL.

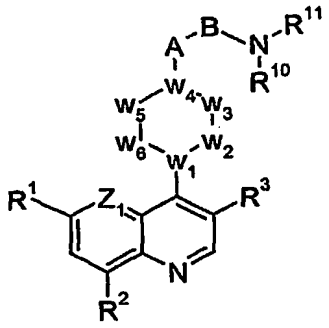
Rat Infection Model:

Specific pathogen-free male Sprague–Dawley CD rats were used for all bacterial strains. Food was removed approximately 18hr prior to infection and replaced immediately following the second dose (7hr post infection). Each therapy group consists of 5 animals. Infection was carried out by intrabronchial instillation of 100ul bacterial suspension via non-surgical intubation. All compounds were administered at 1, 7, 24 and 31hr post infection via oral gavage. In each experiment, an additional group of animals was included and served as untreated infected controls. Approximately 17hr after the end of therapy, the animals were killed and their lungs excised and enumeration of the viable bacteria was conducted by standard methods. The lower limit of detection was 1.7 log10 CFU/lungs.

PU60160p

What is claimed is:

1. A compound of formula (I)



(I)

wherein:

Z_1 is N or CR^{1a};

R^1 and R^{1a} are independently hydrogen; hydroxy; (C_{1-6})alkoxy unsubstituted or substituted by (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; halogen; (C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethyl; trifluoromethoxy; nitro; azido; cyano; acyl; acyloxy; acylthio; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups; or R^1 and R^{1a} may together form ethylenedioxy;
with the proviso that when Z_1 is CR^{1a} then R^1 is not H;

R^2 is H or halogen;
with the proviso that when Z_1 is N, then R^2 is H;

R^3 is hydrogen; halogen; hydroxy; cyano; CF_3; nitro; azido; acyl; aryl; heteroaryl; CO_2H; acyoxy; acylthio; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-

substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{3-7})cycloalkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethoxy; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; or arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

w_1 is N, C, or CR^4;
w_2 is C=O, CR^4, or CR^4R^5;
w_3 is C=O or CR^4R^5;
w_4 is N or CR^4;
w_5 is C=O or CR^4R^5;
w_6 is C=O, CR^4, or CR^4R^5;

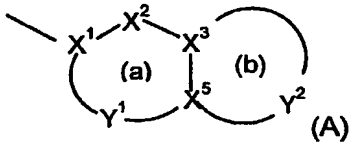
each R^4 and R^5 is independently hydrogen; halogen; hydroxy; cyano; CF_3; nitro; azido; acyl; aryl; heteroaryl; CO_2H; acyoxy; acylthio; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{3-7})cycloalkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethoxy; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; or arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups; or two R^5 groups are joined together to form bicycloheptane;

A is CR^6R^7 or C(O);
B is CR^8R^9 or C(O);

R^6, R^7, R^8, and R^9 are independently hydrogen; halogen; hydroxy; cyano; CF_3; nitro; azido; acyl; aryl; heteroaryl; CO_2H; acyoxy; acylthio; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstitued or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{1-6})alkoxy unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, guanidino or amidino any of which is unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, $CONH_2$, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy or (C_{1-6})alkylsulphonyloxy; (C_{3-7})cycloalkyl; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylthio; trifluoromethoxy; (C_{1-6})alkylsulphonyl; (C_{1-6})alkylsulphoxide; arylsulphonyl; or arylsulphoxide; or an amino, piperidyl, guanidino or amidino group unsubstituted or N-substituted by one or two (C_{1-6})alkyl, acyl or (C_{1-6})alkylsulphonyl groups;

R^{10} is hydrogen; aryl; heteroaryl; (C_{1-6})alkyl unsubstituted or substituted by one or two (C_{1-6})alkoxy, hydroxy, amino, piperidyl, piperazinyl, morpholino, guanidino, or amidino, any of which is unsubstituted or N-substituted by one or two aryl, heteroaryl, halogen, cyano, CF_3, unsubstituted (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, arylsulphonyl, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy, or (C_{1-6})alkylsulphonyloxy, so long as the substitution does not lead to an unstable compound; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; hydroxy-substituted(C_{1-6})alkyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenylcarbonyl; (C_{1-6})alkoxycarbonyl; CO_2H; or CF_3;

R^{11} is a group -U-R^{12} where R^{12} is a substituted or unsubstituted bicyclic carbocyclic or heterocyclic ring system (A):



(A)

containing up to four heteroatoms in each ring in which

at least one of rings (a) and (b) is aromatic;

X^1 is C or N when part of an aromatic ring or CR^{14} when part of a non aromatic ring;

X^2 is N, NR^{13}, O, $S(O)_x$, CO or CR^{14} when part of an aromatic or non-aromatic ring or may in addition be $CR^{14}R^{15}$ when part of a non aromatic ring;

X^3 and X^5 are independently N or C;

Y^1 is a 0 to 4 atom linker group each atom of which is independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring,

Y^2 is a 2 to 6 atom linker group, each atom of Y^2 being independently selected from N, NR^{13}, O, $S(O)_x$, CO and CR^{14} when part of an aromatic or non-aromatic ring or may additionally be $CR^{14}R^{15}$ when part of a non aromatic ring;

each of R^{14} and R^{15} is independently selected from: H; (C_{1-4})alkylthio; halo; (C_{1-4})alkyl; (C_{2-4})alkenyl; hydroxy; hydroxy(C_{1-4})alkyl; mercapto(C_{1-4})alkyl; (C_{1-4})alkoxy; trifluoromethoxy; nitro; cyano; carboxy; amino or aminocarbonyl unsubstituted or substituted by (C_{1-4})alkyl.

each R^{13} is independently H; trifluoromethyl; (C_{1-4})alkyl unsubstituted or substituted by hydroxy, carboxy, (C_{1-4})alkoxy, (C_{1-6})alkylthio, halo or trifluoromethyl; (C_{2-4})alkenyl; or aminocarbonyl wherein the amino group is optionally substituted (C_{1-4})alkyl;

each x is independently 0, 1 or 2;

U is CO, SO_2, CH_2, or $CR^{16}R^{17}$;

R^{16} and R^{17} are independently selected from H; aryl; heteroaryl; (C_{1-6})alkyl; (C_{1-6})alkyl substituted by (C_{1-6})alkoxy, hydroxy, amino, piperidyl, piperazinyl, morpholino, guanidino, or amidino, any of which is substituted or N-substituted by one or two H, aryl, heteroaryl, halogen, cyano, CF_3, (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, arylsulphonyl, hydroxy, (C_{1-6})alkylthio, heterocyclylthio, heterocyclyloxy, arylthio, aryloxy, acylthio, acyloxy, or (C_{1-6})alkylsulphonyloxy, so long as the substitution does not lead to an unstable compound; (C_{1-6})alkoxy-substituted(C_{1-6})alkyl; hydroxy-substituted(C_{1-6})alkyl; amino-substituted(C_{1-6})alkyl, which is N-substituted by one or two (C_{1-6})alkyl, acyl, (C_{1-6})alkylsulphonyl, or arylsulphonyl; (C_{1-6})alkylcarbonyl; (C_{2-6})alkenylcarbonyl; (C_{1-6})alkoxycarbonyl; CO_2H; or CF_3;

or a pharamceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is F, Cl, OCH_3, methyl, or SCH_3.

3. A compound according to claim 1 R^{1a} is H, OCH_3, $OCH_2CH_2OCH_3$.

4. A compound according to claim 1 wherein R^2 is H or F.

5. A compound according to claim 1 wherein R^3 is Cl or F.

6. A compound according to claim 1 wherein each R^4 is independently H, OH, OCH_3, or CH_2OH.

7. A compound according to claim 1 wherein R^5 is H.

8. A compound according to claim 1 wherein the group –U– is $–CH_2–$.

9. A compound according to claim 1 wherein R^{12} is:
benzo[1,2,5]thiadiazol-5-yl;
4H-benzo[1,4] thiazin-3-one-6-yl;
2,3-dihydro-benzo[1,4]dioxin-6-yl;
benzo[1,2,3]thiadiazol-5-yl;
3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl;
7-fluoro-3-oxo-3,4-dihydro-2H-benzo[1,4] oxazin-6-yl;
2-oxo-2,3-dihydro-1H-pyrido[2,3-b][1,4]thiazin-7-yl;
2,3-Dihydro-[1,4]dioxino[2,3-c]pyridin-7-yl;
3-oxo-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazin-6-yl;
[1,2,3]thiadiazolo[5,4-b]pyridin-6-yl;
3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl;
7-chloro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl; or
7-fluoro-3-oxo-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]thiazin-6-yl.

10. A compound according to claim 1 which is:
6-({2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-

{2-[1-(6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}amine;

6-({2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-{2-[1-(6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}amine;

6-({2-[1-(3-chloro-6-methoxy-[1,5]quinolin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(3-chloro-6-methoxy-[1,5]quinolin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[1-(3-chloro-6-methoxyquinolin-4-yl)piperidin-4-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine;

6-({2-[1-(3-chloro-6-methoxy-[1,5]naphthyridin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[1-(3-chloro-6-methoxy-[1,5]naphthyridin-4-yl)phenyl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[1-(3-chloro-6-methoxynaphthyridin-4-yl)piperidin-4-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine;

6-({2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)-

{2-[4-(6-methoxyquinolin-4-yl)piperizin-1-yl]ethyl}amine;

6-({2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

(2,3-dihydro-[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)-{2-[4-(6-methoxynaphthyridin-4-yl)piperizin-1-yl]ethyl}amine;

6-({2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[4-(3-chloro-6-methoxyquinolin-4-yl)piperazin-1-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine;

6-({2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]oxazin-3-one;

6-({2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethylamino}methyl)-4*H*-pyrido[3,2-*b*][1,4]thiazin-3-one;

{2-[4-(3-chloro-6-methoxynaphthyridin-4-yl)piperazin-1-yl]ethyl}-(2,3-dihydro[1,4]dioxino[2,3-*c*]pyridin-7-ylmethyl)amine; and

6-({2-[4-(6-Methoxy-[1,5]naphthyridin-4-yl)-3,6-dihydro-2 H -pyridin-1-yl]-2-oxo-ethylamino}-methyl) -4 H -pyrido[3,2-b][1,4]thiazin-3-one;
or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

13. A method of treating bacterial infections in mammals which comprises administrating to a mammal in need thereof an effective amount of a compound according to claim 1.

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ABSTRACT OF THE DISCLOSURE

Quinoline and naphthyridine derivatives useful in the treatment of bacterial infections in mammals, particularly humans.

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